# War Section.

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## Bismuth in the Treatment of Syphilis.

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IN 1916 Sauton and Robert successfully treated the spirillosis of fowls with bismuth. Sazerac and Levaditi confirmed this work four years later, and if we exclude a few isolated experiments by other workers, we can date the serious study of the treatment of syphilis by bismuth from the year 1920. Since Sazerac and Levaditi published their researches carried out from 1920 to 1922, reports have been forthcoming from almost every medical school in Europe and America. Numerous workers have published a very large number of papers, nearly all of which are the result of investigations upon a small number of cases. These reports make happy reading, many are eulogistic in the highest degree, and some would almost have us believe that the work of Ehrlich is already a "back number." In other words, it seems to me, that bismuth is no exception to the general rule—a new remedy—a new enthusiasm.

On one point the majority of these observers agree: that the spironematicidal effect is slow. The most diverse claims have been made as to the effects of bismuth on the Wassermann reaction. With few exceptions, bismuth has been acclaimed a powerful influence in keeping negative early sero-negative cases (an effect which, as you are well aware, is by no means always obtained by intensive courses of neosalvarsan), and in rendering negative both early and late serum-positive cases, and in keeping such cases negative.

No great importance need be attached to this last claim, viz., the permanence of the negative reaction, since none of these cases can have been followed up for any great length of time.

Excellent results have been reported in the resolution of the inoculation lesions and of the skin and mucous membrane lesions of the early and late manifest stages. There appears to be no definite evidence as to the effect of bismuth on the cytology and Wassermann reactions of the cerebro-spinal fluid, and I regret that I am unable to throw any light upon this problem. I am not convinced that we are justified in withholding intensive arsenical therapy in these cases, especially in early cerebro-spinal involvement, and in treating such a serious complication with a drug which has not yet established itself in this respect. There are meagre reports of "benefit" and "relief" in cases of tabes and general paralysis. A perusal of the literature does not convince me that the results obtained in neuro-syphilis are superior to or equal to those obtained by salvarsan, or even by mercury and the iodides.

This is a very brief and, I hope, a fair *résumé* of the state of affairs when we commenced our investigations at Haslar.

Surgeon Lieut.-Commander P. W. Carruthers was associated with me until October last year, and more recently Surgeon Lieut.-Commander J. B. Crawford. Both these officers helped me ungrudgingly, and the work of which I am to speak to-night is as much theirs as mine.

Treatment was commenced in March, 1923, sodium and potassium tartro-bismuthate being used at first. Owing to the unsatisfactory results obtained with these preparations, metallic bismuth cream has been used since April, 1923. This preparation contains 0·15 grm. metallic bismuth in each cubic centimetre; the composition of the cream being otherwise the same as Lambkin's mercurial cream, viz., a creo-camph. and paraffin base of suitable melting point (37° C.).

*Disadvantages of the Insoluble Tartro-bismuthate Salts.*

(1) The injections were painful.

(2) There was a considerable variation in the amount of the preparation absorbed. On one occasion the first dose (1 c.c.) injected fourteen days previously into the right buttock, oozed out of the needle which had been plunged into the same buttock before injecting the third dose. No absorption had taken place in fourteen days.

(3) The spironematicidal effect was very feeble. *S. pallida* persisted or returned after a temporary disappearance.

(4) Not once did a commencing sero-negative Wassermann case remain negative. All such cases became positive during treatment.

(5) The effect on manifest lesions was certainly greater than that of mercury, but inferior to that of metallic cream, and greatly inferior to that of arsenical preparations.

Fifty-seven men have been treated with metallic bismuth; 567 injections were given.

*Technique of Injections.*

These are given into the buttock in precisely the same manner as mercurial injections—once a week (1 c.c.), a total of 1·2 grm. metallic bismuth being administered in eight weekly injections. Strict asepsis must be maintained. The following are the details of the technique:—

(1) The patient stands in a good light.

(2) The skin over the site of the injection is cleansed by rubbing vigorously with a swab soaked in ether or lysol.

(3) The needle must be inspected to make sure that its lumen is patent and that its eye is free from cotton threads, &c. It is then plunged deeply into the upper and outer part of the buttock and must be left *in situ* at least thirty seconds, *to make sure that it is not in the lumen of a blood-vessel.* This is a vital point in the technique, since metallic bismuth is extremely toxic if injected into the circulation. Should blood exude from or well up in the needle, the needle must be withdrawn, and a fresh one plunged into a new site.

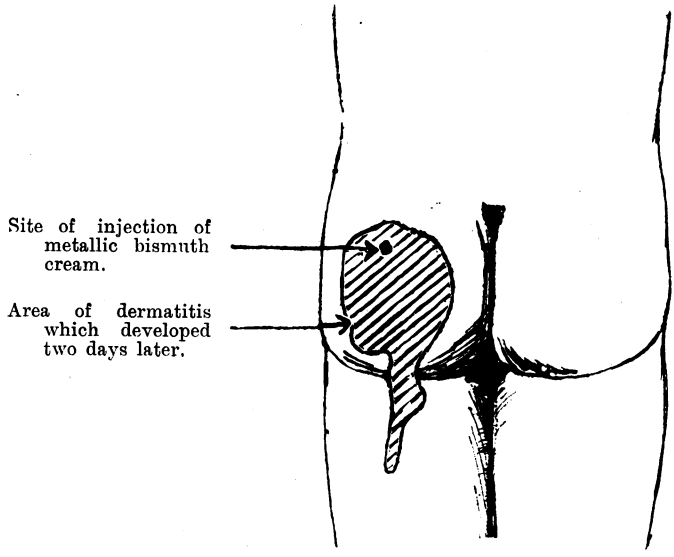
(4) During the short delay of thirty seconds or so, referred to above, the syringe can be filled with the cream. In cold weather it has been found necessary to stand the jar of cream in hot water, as the melting point is approximately that of the body temperature, and it is necessary to stir vigorously before each filling of the syringe. When it is filled, attach the syringe to the needle already in the buttock and inject slowly.

(5) Withdrawal of the needle should be effected in such a way as to block off its path, to obviate tracking back of the cream to the skin. This is best accomplished by pinching the skin beyond the point of the needle as it is withdrawn.

In actual practice it has been found that this step is not so important as it was with mercurial injections, as the bismuth cream is not irritating to the skin and subcutaneous tissues.

(6) Immediately after injection the buttock is massaged vigorously and the

patients elect to go for a brisk walk to work off the slight feeling of stiffness, which invariably resolved in less than an hour. The injections were painless, and in no case has a patient complained of discomfort after walking off the stiffness, nor have any refused treatment.



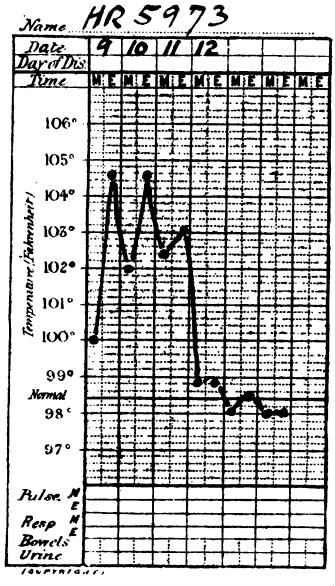




Diagram and Chart illustrating the toxic effects produced in a patient treated with metallic bismuth cream.

No complications other than syncope during injections have been experienced. Syncope is no more common than under any other minor surgical procedure. Two cases (in 567 injections) occurred.

*Toxic Effects.*

Provided the cream be not injected into the general circulation, serious toxic effects are not experienced. Minor toxic effects noted were tenderness and œdema of the gums, usually associated with a black line on the anterior and sometimes on the posterior surfaces of the gums around the upper and lower incisors. Such a black line without symptoms is of no significance.

Serious toxic manifestations occurred in one case only. This patient, admitted on March 15, 1923, was a sero-negative primary case (*S. pallida* was positive). He was given tartro-bismuthate as follows:—

March 16, 1 c.c.; March 18, 1·5 c.c.; March 22, 2 c.c.; March 26, 2 c.c.

*S. pallida* was still present on March 21, but absent on March 26.

On April 7, 1 c.c. of metallic bismuth cream was injected. On the morning of April 9 his temperature was 100° F. The gums were œdematous and septic and an area of œdematous dermatitis, of the shape and size shown in the accompanying diagram, developed round the site of injection. The pyrexia lasted three days (see chart), and during that time the patient was extremely ill.

*The symptoms and signs were:* Pain in the throat and submaxillary glands (both glands were greatly enlarged). There was a well marked dark bluish-black line on the anterior and posterior aspects of the gums around the upper and lower incisors. The fauces were congested. Vomiting occurred twice on April 9.

Next day the edges of the œdematous patch on the left buttock were less marked. The temperature rose to 104·6° F. that evening. The gums and submaxillary glands remained as before.

On the eleventh day the gums and glands were resolving, the buttock was less swollen, the local patch of dermatitis had faded and the temperature began to fall. Except for a crop of labial herpes, no further signs occurred and the patient made a complete recovery, being discharged to duty on April 20.

There was no evidence at the time of injection that the drug had been forced into a vessel.

*Effect on Spironemes.*

Five cases of early syphilis were treated; all were "A" type cases (*S. pallida* positive—Wassermann negative). Treatment was abandoned after five injections in two cases, and after three injections in three cases, novarsenobillon being substituted.

From these cases it became evident that the spironematicidal effect is feeble compared with that of arsenical drugs given intramuscularly. In one case the *S. pallidæ* was found twenty-four hours after the first injection, but were absent forty-eight hours afterwards. Twenty-four hours after a second dose, given seven days later, this organism was however again present. In the remaining cases *S. pallida* was found daily for an average period of one week. The spirochætes were not demonstrated later than one week.

*Effect on the Wassermann Reaction in the Serum.*

All the five negative-serum cases became positive during treatment. (One case developed "secondaries" whilst under treatment.) Further treatment by bismuth alone was not considered justifiable in early syphilis, and was abandoned.

On account, however, of its beneficial effect upon the manifest lesions of syphilis, I decided to confine its use to: (1) Old cases which had nearly all been treated with several courses of novarsenobillon and had persistent positive

Wassermann reactions; (2) cases intolerant of arsenical drugs, as proved by repeated toxic reactions which rendered further arsenical treatment unsafe; (3) cases unsuitable for arsenical treatment; (4) cases with jaundice, due to arsenical preparations.

(1) Twenty-nine cases of latent syphilis with positive Wassermann reactions were treated. All appeared to be in good health. Five cases had cerebro-spinal involvement. (Three showed excess of lymphocytes only and two had in addition a positive Wassermann reaction in the cerebro-spinal fluid.) In one case only has the Wassermann reaction in the serum become negative (patient had been under arsenical treatment quite recently). In all the others it has remained positive or reverted to positive after one or more weak positive findings. It is hardly necessary for me to remind you that the serological findings in old cases are variable, even without treatment, and that syphilis does occasionally tend to resolve spontaneously without treatment.

I think we are justified, as far as *any* conclusions can be drawn from an eight to ten months' observation of a few cases, in assuming that no striking effect on the serum Wassermann in latent cases can be expected from bismuth. In judging its effect upon cerebro-spinal lesions, we must not jump at conclusions unless definite facts are established from an observation of a very large series of cases.

(2) *Cases Intolerant of Arsenical Drugs.*—Eleven cases which had exhibited one or more toxic reactions were treated. It is impossible to decide to what extent bismuth was responsible for their after-history, since it is within common knowledge that cases which have received only three or four injections of an arsenical compound may remain negative and free from symptoms for years, or, again, may relapse serologically and clinically.

One early positive case of manifest syphilis received three doses of 0·45 grm. novarsenobillon. The third dose gave rise to a severe toxic reaction (pyrexia for four days, severe pains in the head and chest, erythema, colic, melæna, diarrhœa, and suffusion of the right conjunctiva). This dose was given on June 1, 1923, the Wassermann reaction having been found positive on May 24, 1923. Bismuth treatment commenced on June 19, 1923. The Wassermann reaction on August 21, 1923, was negative, this being probably due to the novarsenobillon.

No conclusions as to the effect of bismuth on the Wassermann reaction can be formed from these eleven cases. All of them tolerated bismuth well.

(3) One case of aortitis, in which the patient had heen very distressed by small doses of novarsenobillon, tolerated and derived some benefit from bismuth. The positive Wassermann reaction was unaffected. A trace of bile pigment was detected in the urine during the short novarsenobillon course.

(4) Three cases of jaundice due to novarsenobillon were treated. The Van den Bergh test showed indirect biphasic reactions. The bilirubin was not estimated in one case; there were eight and four units of bilirubin respectively in the other two cases. All tolerated bismuth well, but in none was the positive Wassermann reaction altered.

Two other cases of jaundice, complicated by manifest lesions, will be referred to later.

*Effects upon the Manifest Lesions.*

There is a definite superiority over mercury in the effect of bismuth upon early and late manifest lesions. A striking example of this is demonstrated by the following cases:—

(*a*) An aircraftsman was admitted on February 25, 1923, suffering from florid manifest syphilis. He was deeply jaundiced. He was originally infected in

December, 1921, and received four courses of novarsenobillon, the last being in November, 1922. His Wassermann reaction had never been found negative; on March 1, 1923, it was positive.

Examination showed moist papules in coronal sulcus and in the fossa navicularis; mucous patches of buccal mucous membrane and of tongue; general adenitis; papulo-squamous syphilide. The Van den Bergh test gave a biphasic reaction and showed four units of bilirubin. Bile salts and pigments were present in the urine. The liver was definitely enlarged and tender. Mercury was given orally up to March 20. The florid lesions of syphilis were still florid and a macular syphilide developed between the papular lesions. Bismuth injections were begun on March 20. By April 5 the patient was discharged from hospital, all lesions and the jaundice having completely resolved. The jaundice was treated by intravenous injections of collosal iodine. He attended weekly for further treatment up to June 24, receiving in all twelve injections (three of tartro-bismuthate and nine of metallic bismuth cream). On September 5 he commenced a second course. He was then the picture of health, and had gained 14 lb. in weight. The liver was not enlarged. Wassermann, June 6 and September 5, 1923, positive. After receiving six more injections he was drafted abroad.

(*b*) Another case was that of a chief petty officer (now pensioned) who contracted syphilis in 1894. For the last three years he had been treated for dermatitis of both hands. He was sent to me on May 1. He had a serpiginous squamous syphilodermia of the dorsa of both hands. Eight weekly injections of bismuth cream were given. Sixteen days after the first injection the condition had completely resolved. Wassermann positive before and after treatment, but became weakly positive during the course.

(*c*) A patient who had syphilis in 1916 presented a serpiginous squamous syphilide of the scrotum, which resolved in ten days. Five months from the commencement of treatment the Wassermann was weakly positive, four previous tests since 1916 having been positive.

(*d*) A case of syphilis of twenty years' duration with positive Wassermann and leukoplakia at the right angle of the mouth, showed complete resolution of this lesion when the patient presented himself for the second course of bismuth. Seven months from the date of the first injection the Wassermann was still positive. One further case is of special interest as it demonstrates the failure of mercury clinically and the success of bismuth.

He was infected in October, 1921, but did not originally come under treatment until January, 1922, when he was in the florid manifest stage of skin lesions. The course of N.A.B. (4·2 grm. in twenty-eight days) was followed by another (2·7 grm.) in June, 1922; the Wassermann was still positive at the end of the second course. On presenting himself three months later for the third course, viz., in September, 1922, he was found to be intensely jaundiced (12 units of bilirubin). Mercury treatment was advised. From October, 1922, to January, 1923, and again from February to May, 1923, he was under continuous mercury treatment in the ship. On June 5, 1923, he was sent to Haslar with florid manifest syphilis of skin and mucous membranes. There was marked general glandular enlargement. Wassermann positive. Metallic bismuth injections were commenced on June 6. The mucous membranes were clear in a fortnight, and on discharge from hospital there was a very faint trace of the skin lesions. A second course of bismuth was completed on December 12, 1923. The Wassermann up to November, 1923, was positive on six occasions. On December 6, 1923, it was weakly positive.

There can be no question, therefore, that bismuth does exercise a very powerful influence upon the manifest lesions, early and late. It exercises, I think, an infinitely greater effect than that produced by mercury.

## Conclusions.

Metallic bismuth cream cannot be considered comparable to the neo-salvarsan-type drugs. It would appear to occupy a half-way position between mercury and neo-salvarsan, and although inferior in every respect to Ehrlich's preparations, it is decidedly of greater clinical power than mercury.

Compared with mercury, it is: (1) Far less toxic and pleasanter to take. (2) Of greater clinical therapeutic value. (3) Of slightly greater spironematicidal power. (4) Equally ineffective in influencing a positive Wassermann, and in preventing early sero-negative cases from becoming positive.

Bismuth appears to offer a better outlook than mercury in cases which are intolerant of arsenic. It could be given in cases unsuitable for the arsenical preparations, and liable to tolerate them badly, viz.: cases of gross visceral syphilis, aortitis, arsenical jaundice, &c. In certain cases of this type it should prove of value as prodromal treatment, to precede cautious dosage with arsenical drugs.

Lastly, those who favour adjuvant treatment (viz.: mercury plus neosalvarsan) should find a, clinically, more powerful and less toxic ally in metallic bismuth.

## DISCUSSION.

Surgeon-Commander S. F. DUDLEY pointed out how difficult it was to compare the relative efficiency of the different agents used to treat syphilis, when it was not possible to follow large numbers of cases for many years. Especially was this the case as regarded what was probably the most important point of all—the prevention of the late nervous manifestations. He drew attention to the fact that many protozoa could be rendered permanently tolerant of arsenic; and clinical evidence suggested that after a course of arsenical treatment a similar change sometimes occurred in the *Spironema pallidum*. Levaditi had shown it was much more difficult, if not impossible, to produce bismuth resistant trypanosomes, and in this connexion one of the chief points he made for bismuth was the rarity of clinical relapse. If this was confirmed, and should it be found that arsenic-tolerant organisms were still destroyed by bismuth, a valuable use for bismuth was at once evident—a course of arsenic should be followed by one of bismuth in order to destroy any arsenic-resistant spironemes that might have survived. Surgeon-Commander Parnell's "old cases" which, in spite of much arsenic treatment, refused to clear up until they subsequently received bismuth constituted strong support of the hypothesis that some relapses were due to arsenic-tolerant spironemes. He (Surgeon-Commander Dudley) also drew attention to Levaditi's new preparation (bismoxyl), a complex of tissue extracts and bismuth which the French workers claimed to be much superior to metallic bismuth or its salts. This seemed reasonable, if it was true that metals had to form a protein complex in the body before they could function as parasiticides.

For these reasons he (Surgeon-Commander Dudley) considered that if a suitable protein bismuth preparation could be obtained, further researches should be undertaken to compare its action with that of the older bismuth and arsenical drugs before definitely placing bismuth second to arsenic in the treatment of syphilis.

Major FROST said that he was very glad to hear Surgeon-Commander Parnell's paper on the use of bismuth alone in the treatment of syphilis, as in the Army the drug had been used in conjunction with arsenic. Both at the Military Hospital, Rochester Row, and at the Royal Herbert Hospital, Woolwich, this combination had given satisfaction. It was felt that the combination of bismuth and stabilarsin was the most efficient means of treating syphilis at the present day. Cases which were negative to the Wassermann reaction before the beginning of treatment remained negative, and cases which gave a positive reaction became negative in about 80 per cent. of the cases at the end of the first course, and had remained so. A number of bismuth preparations had been tried during the last year in order to find out which was the best for military conditions. As the value of the drug resided, like mercury, in its metal content, it was felt that the choice lay between the suspended, finely divided metal such as the group of which neotrepol and bismuthyl were examples, or the oxychloride like bischlorol. The weekly dose of the former was 0·2 grm. and of the oxychloride was 0·16 grm. of the metal, each in 2 c.c. of fluid. The suspended metal was painless if given deeply into the muscles, but it caused pain if it leaked into the subcutaneous tissues. The oxychloride, it was found, could be injected into the deep subcutaneous tissues without pain and X-ray examination showed a steady absorption of the deposit, the oldest of

five injections being a slight shadow, the others shading up to a deep black shadow of the most recent one. In cases of intolerance to arsenic he wished to warn against too early use of bismuth in continuing treatment as this drug also was capable of producing skin lesions. In the treatment of nervous cases of syphilis, especially in the reduction of crisis in tabes, bismuth was, he found, superior to arsenic.

The future position of bismuth would be as an adjuvant to arsenic in the treatment of syphilis, to the exclusion of mercury.

Dr. F. CARMINOW DOBLE said he considered that bismuth came between arsenic and mercury in the treatment of syphilis, and that the patient stood bismuth better than either of the other drugs. He found that if bismuth alone was given the spironema was present in the lesions for at least fourteen days, therefore arsenic must be given so as to render the patient non-infectious with the least possible delay. He was of the opinion that these two drugs should be given during the whole course of treatment, unless arsenic was contra-indicated. The makers of several well-known brands had informed him that they would not send the drug out in large containers, but only in ampoules, as the presence of air caused the salt of bismuth to split up, and also it was impossible to be certain that the drug was properly mixed, the heavy metal falling to the bottom of the jar. As regards the brand, he was very favourably impressed with bischlorol, spirillan and bismuthyl.

He gave the drug by deep subcutaneous injections, either in the upper and outer quadrant of the buttock or between the shoulder blades. The injections were painless, and he had given them to boxers and football players just before an important match without any complaints. In the case of jaundice after "914" he had had two patients who gave a strongly positive Wassermann reaction after the jaundice had disappeared; these cases gave a negative Wassermann after two months' treatment with bismuth, although they had twelve and sixteen injections of arsenic respectively without affecting the reaction. A singer who was being treated with arsenic and mercury complained that his voice was being affected by the mercury. When this was stopped he said that the arsenic was responsible. On being treated with bismuth only, he stated that his voice was splendid, but he (Dr. Doble) had not heard a sample of his singing.

Dr. H. SEMON remarked that there was a very serious discrepancy in the results of Surgeon-Commander Parnell and Dr. Sazerac and Dr. Levaditi. It was the duty of all investigators to do their utmost to find an alternative to arsenic medication, for all these compounds were dangerous, even in skilled hands. He mentioned a new antidote—thiosulphate of soda, by intravenous injection, and recommended his hearers to investigate its effects.

Surgeon-Commander PARNELL (in reply) said that he was glad to hear that Major Frost regarded bismuth merely as a substitute for mercury, and as adjuvant treatment to salvarsan. He was not aware that bismuth caused dermatitis, but Major Frost's experience in this respect was a timely warning. He could only assert again that injections of bismuth cream had proved absolutely painless. Perhaps his dosage accounted for the discrepancy between his results and those of Levaditi, quoted by Dr. Semon. At Haslar the course now consisted of two injections of 1 c.c., three of 1·5 c.c., and three of 2 c.c., given at intervals of a week in the case of out-patients, and at intervals of five days in the case of in-patients. He did not consider that a three weeks' interval between injections of salvarsan would obviate toxic reactions. One of the very worst cases of cerebral toxæmia occurred, in his experience, after a second injection administered thirty-four days after the first. He believed that, whatever the intervals, these reactions would occur, and that they could not be foreseen or prevented. Personally, he never exceeded 0·45 grm. as a dose, and he called to mind German statistics which showed that once 0·45 grm. was exceeded, the incidence of toxic effects immediately went up. He would certainly give a trial to the arsenical antidote mentioned by Dr. Semon, viz., thiosulphate of soda.

CORRIGENDUM.

In Colonel Henderson's remarks in the discussion on Major Frost's paper, "Present-day Trend of Treatment of Gonorrhœa," *Proceedings*, January, 1924 (War Section), p. 5, line 6 from bottom, for "lubefacient" read "Lubefax."